

REMARKS

Claims 1-6, 9-13, 17, 24-26, 28-37 and 44-56 were pending. However, claims 24-26 and 53 are withdrawn from consideration as directed to a nonelected invention. Applicants amended claims 1, 3, 9, 17, 30, 34, 35, 50, 52, 55 and 56 and cancelled claims 24-26, 28-29, 31-32 and 53. New claims 57-63 were added. Accordingly, only claims 1-6, 9-13, 17, 30, 33-37, 44-52, and 54-63 are pending.

Support for amended claims 1, 3, 9, 17, 30, 34, 35, 50, 52, 55 and 56 and new claims 57-63 may be found in the claims and specification as originally filed. Accordingly, these changes do not involve new matter and Applicants respectfully request entry of these changes.

The amendment made to withdrawn claim 52 is merely to correct the dependency.

Support for amended claim 1 may be found in the specification as originally filed at page 26, lines 9-15; page 47, Example 1 and originally filed claim 3.

Support for amended claim 3 may be found in the specification as originally filed at page 26, lines 9-15.

Support for amended claim 9 may be found in the specification as originally filed at page 7, lines 10-18; page 25, lines 29-31; and page 26, lines 1-7.

Support for amended claim 17 may be found in the specification as originally filed at page 7, lines 10-18; and page 26, lines 9-15.

Support for amended claim 30 may be found in the specification as originally filed at page 27, lines 30-31 continuing to page 28, lines 1-5 and originally filed claims 31 and 32.

Support for amended claim 34 may be found in the specification as originally filed at page 47, Example 1.

Support for amended claim 35 may be found in the specification as originally filed at page 30, lines 9-16.

Support for amended claim 50 may be found in the specification as originally filed in SEQ ID NO.4.

Support for amended claim 55 may be found in the specification as originally filed at page 31, lines 9-16.

Support for amended claim 56 may be found in the specification as originally filed at page 31, lines 9-16 and Figure 15.

Support for new claim 57 may be found in the specification as originally filed at page 27, lines 15-28; page 30, lines 18-26; and page 47, Example 1.

Support for new claim 58 may be found in the specification as originally filed at page 27, lines 15-28; page 30, lines 18-26; and page 47, Example 1.

Support for new claim 59 may be found in the specification as originally filed at page 47, lines 10-17.

Support for new claim 60 may be found in the specification as originally filed at page 47, lines 10-17.

Support for new claim 61 may be found in the specification as originally filed at page 54, Example 5.

Support for new claim 62 may be found in the specification as originally filed at page 7, lines 10-18; and originally filed claim 34.

Support for new claim 63 may be found in the specification as originally filed at page 7, lines 10-18; and originally filed claim 1.

In accordance with the changes to the claims and the remarks that follow, Applicants respectfully request reconsideration of the outstanding rejections.

ITEM 1: APPLICANT'S AMENDMENTS

The Office acknowledges the amendments filed by the Applicants on November 12, 2004 and claims 1-6, 9-13, 17, 24-26, 28-37 and 44-56 are pending. No response is due.

ITEM 2: SPECIES ELECTION

The Office acknowledges the Applicant's election of the following species with traversal:

- the alkylating agent is busulfan;
- the first ligand is soluble CTLA4;
- the second ligand is anti-CD40 antibody, and
- the targeted condition is solid organ or tissue/cellular transplant.

Regarding claims 24-26 and 53, the Office alleges that these claims are drawn to non-elected species, and therefore are withdrawn from further consideration. Therefore, only claims 1-6, 9-13, 17, 28-37, 44-52 and 54-56 are being examined in the instant application, to the extent that they read on the elected species.

ITEM 3: COMPLIANCE WITH THE SEQUENCE RULES

In item 3 of the Office Action, the Office indicated that the subject application is not in compliance with the sequence rules. In particular on page 79, where the sequence “MYPYY” is missing a sequence identifier. In response, Applicants have amended the specification to include sequence identifiers, see supra.

ITEM 4: PRIORITY

At the outset, the Office indicated that the priority application, U.S. Serial No. 60/264,528, filed January 26, 2001, does not support “the instant claims encompassing methods of inhibiting rejection of a solid organ or tissue/cellular transplant by administering an alkylating agent (e.g. busulfan) and subsequently administering T cell depleted bone marrow cells before, during or after as the transplant, as well as administering CD28/CD80/CD86/CD154/CD40 inhibitors” (Office Action at page 2, second full paragraph of Section 4).

But the Office has taken the position that the filing date of the instant claims is deemed to be the filing date of priority application U.S. Serial No. 60/303,142, filed July 5, 2001.

Applicants respectfully disagree.

CONTRARY TO THE OFFICE'S POSITION, APPLICANTS ARE ENTITLED TO THE JANUARY 26, 2001 FILING DATE

Specifically, support for the claims being examined may be found in U.S. Serial No. 60/264,528, at page 4, 1st full paragraph and page 5, 1st full paragraph, and Figures 2A and 2B, wherein Applicants' data successfully demonstrated the inhibition of transplant rejection by a method comprising administering to a subject (a mouse) a dose of T cell depleted bone marrow, followed by busulfan and an immunosuppressive composition (Figures 2A and 2B).

ITEM 5: TITLE

The Office alleges that the title of the subject application is not descriptive. The Office requires a new title, restricting the title to the claimed invention.

In compliance with the Office's request, the Applicants have amended the title, see supra.

ITEM 6: ABSTRACT OF THE DISCLOSURE

The Office objects to the abstract because it does not adequately describe the claimed invention.

In compliance with the Office's request, Applicants have amended the abstract, see supra.

ITEM 7: SPELLING

In item 7 of the Office Action, the Office suggests correcting all spelling errors and indicating trademarks, where appropriate. In response, Applicants have made the corrections hereinabove.

ITEMS 8 AND 9: REJECTION UNDER 35 U.S.C. §112 FIRST PARAGRAPH

The Office rejects claims 45-50 and 56 under 35 U.S.C. §112 first paragraph because the specification, while enabling for “the specific mutant CTLA4 molecules such as the L104EA29YIg molecule disclosed in the specification as filed or claimed (e.g., see Example 8 on pages 67-83 of the instant specification), does not reasonably provide enablement for any “CTLA4 mutant molecule” to be employed as an immunosuppressive agent in the instant claimed methods.”

Applicants respectfully disagree.

The term “CTLA4 mutant molecule” is definite. For example, CTLA4 mutant molecule “means wildtype CTLA4 as shown in Figure 19 or any portion or derivative thereof, that has a mutation or multiple mutations (preferably in the extracellular domain of wildtype CTLA4). A CTLA4 mutant molecule has a sequence that it is similar but not identical to the sequence of wild type CTLA4 molecule, but still binds a B7. The mutations may include one or more amino acid residues substituted with an amino acid having conservative (e.g., substitute a leucine with an isoleucine) or non-conservative (e.g., substitute a glycine with a tryptophan) structure or chemical properties, amino acid deletions, additions, frameshifts, or truncations. CTLA4 mutant molecules may include a non-CTLA4 molecule therein or attached thereto. The mutant molecules may be soluble (i.e., circulating) or bound to a cell surface. Additional CTLA4 mutant molecules include those described in U.S. Patent Application Serial Numbers 09/865,321, 60/214,065 and 60/287,576; in U.S. Patent Numbers 6,090,914 5,844,095 and 5,773,253; and as described by Peach, R. J., et al., in *J Exp Med* 180:2049-2058 (1994)). CTLA4 mutant molecules can be made synthetically or recombinantly (specification at page 19, lines 6-19).”

Further, Applicants provided examples of six CTLA4 mutant molecules including their entire nucleotide sequence and described the required functions for other members of the class of proteins provided by the invention.

35 U.S.C. § 112, first paragraph, requires Applicants to teach how to make and use the invention, without undue experimentation. The law is clear. Applicants are not required to disclose every species encompassed by the claims (*In re Angstadt and Griffin*, 190 USPQ 215, 218 CCPA 1976)). Moreover, despite the fact that Applicants do not disclose every known CTLA4 mutant molecule, the identification of other species in the class would not entail undue experimentation because Applicants' disclosure outlines a number of different assays for the identification of CTLA4 mutant molecule as claimed. Practice of the claimed invention does not require undue experimentation.

In view of the preceding remarks, Applicants respectfully request that the Office reconsider and withdraw the various grounds for objection and rejection set forth in the Office Action.

ITEM 10: REJECTION UNDER 35 U.S.C. §112 FIRST PARAGRAPH

The Office rejects claims 50 and 56 under 35 U.S.C. §112 first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. In particular, the Office is requiring Applicants to provide assurance that the ATCC deposit of the DNA composition be made readily obtainable to the public.

In response, Applicants provide the following statement of assurance.

Statement of ATCC Deposit:

Applicants' patent representative maintains that the plasmid DNA disclosed in the present application is the same as that designated ATCC Accession No. PTA-2104 which has been deposited pursuant to the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure with the Patent Culture Depository of the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, Virginia 20110-2209 U.S.A. on June 19, 2000. Applicants provide a copy of a Receipt Form issued by the American Type Culture Collection, confirming deposit of PTA-2104 (Exhibit A).

Accordingly, Applicants maintain that during the pendency of the present application, access to the ATCC deposit will be afforded to one determined by the Commissioner to be entitled thereto under 35 U.S.C. §1.14 and §122, and all restrictions on the availability to the public of the material deposited under ATCC Accession No. PTA-2104 will be irrevocably removed upon the issuance of a patent from the present application. Furthermore, the above deposits will be maintained by the ATCC for a period of 30 years from the date of deposit or at least 5 years after the last request for a sample of the deposited material, whichever is longer. Where the ATCC cannot furnish samples of the above deposits for any reason, Applicants shall make a replacement deposit, of the material which was originally deposited, within three months of receiving notification that the ATCC cannot furnish samples.

ITEM 11: REJECTION UNDER 35 U.S.C. §112 SECOND PARAGRAPH

The Office rejects claims 50 and 56 under 35 U.S.C. §112, second paragraph, as allegedly indefinite in recitation of L104EA29YIg. The Office alleges that L104EA29YIg is merely a laboratory designation which does not clearly define the claimed product.

Applicants respectfully disagree.

The term L104EA29YIg is definite, and is clearly defined at page 20 lines 7-17 in the specification, as originally filed. However, in order to further the prosecution of the subject application, Applicants have deleted the term “L104EA29YIg” in claims 50 and 56 and have replaced the term with a soluble CTLA4 mutant molecule comprising an amino acid which begins with methionine at position 27 and ends with lysine at position 383 as shown in SEQ ID NO:4, or which begins with alanine at position 26 and ends with lysine at position 383 as shown in SEQ ID NO:4.

ITEMS 12 AND 14: REJECTION UNDER 35 U.S.C. §102(e)

The Office rejects claims 1-6, 9-13, 17, 28-29, 34-37, 48 and 51-55 under 35 U.S.C §102(e) as allegedly anticipated by Sykes (U.S. Patent No. 6,514,513) (hereinafter referred to as “Sykes”).

Applicants respectfully disagree. It is Applicants’ position that the present invention is not anticipated by Sykes.

The present invention provides methods for inhibiting rejection of a solid organ or tissue/cellular transplant in a subject comprising: a) administering T cell depleted bone marrow cells to the subject before, during or after the solid organ or tissue/cellular transplant; b) subsequently administering an alkylating agent (e.g., busulfan) to the subject in an amount that facilitates mixed hematopoietic chimerism; and c) administering to the subject an immunosuppressive composition that blocks T cell costimulatory signals in the subject before, during or after the transplant.

THE LEGAL STANDARD FOR NOVELTY

To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either expressly or inherently. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1574, 224 USPQ 409, 411 (Fed. Cir. 1984). Each and every element of the claimed invention must be disclosed in a single prior art reference in a manner sufficient to enable one skilled in the art to reduce the invention to practice, thus placing the invention in possession of the public. *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied* 469 U.S. 851, 105 S.Ct. 172 (1984); *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576-7 (Fed. Cir. 1991), *clarified, on recons.*, 1991 U.S.App. LEXIS 33,486 (Fed. Cir. 1991). The absence of even a single element from a prior art reference negates anticipation. *Atlas Powder Co. v. E. I. Du Pont de Nemours & Co.*, 750 F.2d 1569, 1574 (Fed. Cir. 1984).

To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill, *Continental Can Co. v. Monsanto*, 948 F.2d 1264, 20 USPQ2d 1746 (1991). “Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient.”

APPLICANTS HAVE MET THE LEGAL STANDARD FOR NOVELTY

Sykes discloses methods of inducing tolerance to foreign antigens. The methods feature preparative regimens which may minimize or eliminate the need for thymic irradiation, T cell inhibiting antibodies, and in some cases may eliminate hematopoietic space-creating irradiation, e.g. preparative whole body irradiation (Sykes at column 1, lines 32-36).

Sykes' invention features a method of promoting acceptance, by a recipient mammal, of a graft from a donor mammal of a second species. The method includes: administering to the recipient, an inhibitor, e.g., a blocker, of a costimulatory pathway, (e.g., one or both of, an inhibitor, e.g., a blocker, of the CD40 ligand-CD40 interaction and an inhibitor, e.g., a blocker, of the CD28-B7 interaction); introducing, e.g., by intravenous injection, into the recipient mammal, hematopoietic stem cells, e.g., a bone marrow preparation; and preferably, implanting the graft in the recipient. The hematopoietic cells are believed to prepare the recipient for the graft that follows, by inducing tolerance at both the B-cell and T-cell levels (Sykes at column 1, lines 49-52).

Although Sykes' methods feature preparative regimens which may minimize or eliminate the need for hematopoietic space-creating irradiation, e.g. preparative whole body irradiation, Sykes only uses irradiation in the methods described (Sykes at column 22, lines 36-40; column 23, lines 15-19; column 24, lines 34-36; column 25, lines 9-12; and column 27, lines 52-55).

Busulfan is also disclosed as an alternative to irradiation to create "hematopoietic space" (Sykes at column 5, lines 3-6; column 8, lines 29-32; and column 11, lines 51-54). In either event, Sykes discloses that the step of creating hematopoietic space occurs prior to hematopoietic stem cell transplantation (Sykes at column 4, lines 63-65; column 8, lines 21-23; and column 11, lines 44-45).

Sykes do not expressly anticipate the claimed methods, because Sykes do not expressly or inherently disclose "administering busulfan to the subject *in an amount* that facilitates mixed hematopoietic chimerism" or "administering an alkylating agent to the subject in an amount that facilitates mixed hematopoietic chimerism." Sykes merely suggests that busulfan may be used in lieu of irradiation, to create hematopoietic space. Hence, the

missing element, namely “administering busulfan to the subject *in an amount* that facilitates mixed chimerism” or “administering an alkylating agent to the subject *in an amount* that facilitates mixed chimerism”, is not taught by Sykes. In contrast, the subject application does disclose appropriate doses of busulfan.

Further, Sykes does not inherently anticipate the claimed methods because Sykes does not disclose a correlation between the irradiation dosage disclosed therein to a correlative amount of an alkylating agent (for example, busulfan) that facilitates mixed hematopoietic chimerism.

Further still, in contrast to the claimed methods, Sykes do not anticipate the claimed methods, because Sykes discloses using either irradiation or busulfan prior to the step of hematopoietic stem cell transplantation (Sykes at column 4, lines 63-65; column 8, lines 21-23; and column 11, lines 44-45). In contrast, Applicants teach and claim the use of an alkylating agent such as busulfan after introduction of bone marrow cells.

Therefore, Sykes cannot form the basis for an anticipation rejection under §102(e). Accordingly, Applicants respectfully request that the Office reconsider and withdraw the rejections to claims under 35 U.S.C. §102(e).

ITEMS 13 AND 15: REJECTION UNDER 35 U.S.C. §103(a)

The Office rejects claims 1-2, 9-10, and 30-32 under 35 U.S.C §103(a) as allegedly unpatentable over Sykes et al. ('513 patent) in view of art known practice and modes of administration of alkylating agents such as busulfan.

Applicants respectfully disagree.

The burden is on the Examiner to establish a *prima facie* case of obviousness by showing that the prior art would have taught or suggested the claimed invention to one of ordinary skill in the art, and that one of ordinary skill in the art would reasonably expect that the method suggested by the references would be successful.¹ The Examiner must provide evidence that both the suggestion to modify the prior art method and the reasonable expectation of success can be found in the prior art.² In addition, the prior art must teach or suggest all of the claim limitations.³

Sykes discloses the use of busulfan prior to the hematopoietic stem cells transplantation and not after. Sykes did not disclose or suggest or provide motivation to use busulfan after a hematopoietic stem cell transplantation to introduce hematopoietic chimerism.

Further, although Sykes suggests that busulfan can be used in their methods to create hematopoietic space, Sykes does not teach or suggest any amount of busulfan to create hematopoietic space, let alone in an amount to induce hematopoietic chimerism, so as to provide a reasonable expectation of success, or invitation to try, the use of busulfan after the step of hematopoietic cell transplantation. In fact, there is no data and no elaboration on how and what amounts of busulfan can be used in Sykes, except to state that it can be used prior to the step of hematopoietic stem cell transplantation.

To establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the Applicant.^{4,5} Even when obviousness is

¹ *In re Clinton*, 527 F.2d 1226, 1228, 188 USPQ 365, 367 (CCPA 1976).

² *In re Gangadharam*, 13 USPQ2d 1568, 1569 (Fed. Cir. 1989); *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

³ *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988).

⁴ See *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed.Cir.1998)

⁵ *In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed.Cir.1984)

based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference.⁶

Sykes suggests administering busulfan prior to administering the stem cells. In contrast, the claimed invention provides administering a dose of busulfan after a first dose of T cell depleted bone marrow. There is no suggestion or motivation in the art to change the order in which the alkylating agent is administered in Sykes to accomplish Applicants' claimed invention.

Additionally, not only is Sykes not suggestive of the claimed method, but, in fact, Sykes teaches away from the claimed invention. Specifically, the claimed invention teaches a method for inhibiting rejection of solid organ or tissue transplant comprising administering T cell depleted bone marrow; subsequently administering an alkylating agent (for example, busulfan); and an immunosuppressive composition before, during or after the transplant. The claimed invention specifically teaches administration of an alkylating agent (for example, busulfan) after an administration of T cell depleted bone marrow.

In contrast, Sykes discloses the step of treating the subject with whole body irradiation (or alternatively administering cyclophosphamide or busulfan), to create hematopoietic space, but prior to the hematopoietic stem cell transplantation (see the '513 patent at col 4, lines 60-65, col 5, lines 1-9, col 8, lines 20-32, col 11, lines 42-54). Therefore, Sykes teach away from the steps of the claimed invention, to inhibit rejection of solid organ or tissue transplant rejection.

⁶ See *B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.*, 72 F.3d 1577, 1582, 37 USPQ2d 1314, 1318 (Fed.Cir.1996)

ITEM 16: REJECTION UNDER 35 U.S.C. §103(a)

The Office rejects claims 1, 9 and 33 under 35 U.S.C §103(a) as allegedly unpatentable over Sykes et al. (Sykes) in view of Larsen et al. (US Patent No. 5,916,560) (Larsen).

Applicants respectfully disagree.

Sykes was discussed above.

Larsen et al. teaches compositions and methods of inhibiting an immune response by using a combination of two agents, wherein the first agent blocks the CTLA4/CD28/B7 pathway and the second agent blocks the gp39/CD40 pathway.

Larsen does not teach or suggest what the primary reference fails to teach, namely, use of any amount of any alkylating agent, let alone busulfan, to facilitate mixed hematopoietic chimerism, subsequent to administration of T cell depleted bone marrow, or use of any alkylating agent, after a bone marrow tranplantation. Accordingly, the combination of the Sykes and Larsen references, does not render obvious the claimed methods.

ITEM 17: REJECTION UNDER 35 U.S.C. §103(a)

The Office rejects claims 1, 5, 9, 11, 12, 34-36, 44-52, 54, and 56 under 35 U.S.C §103(a) as allegedly unpatentable over Sykes et al. (Sykes) in view of Peach et al. (US 20020182211) (Peach).

Applicants respectfully disagree.

Sykes was discussed above.

Peach teaches CTLA4 mutant molecules with mutations at position 29 and at position 104.

Peach does not teach or suggest what the primary reference fails to teach, namely, use of any amount of any alkylating agent, let alone busulfan, to facilitate mixed hematopoietic chimerism, subsequent to administration of T cell depleted bone marrow, or use of any alkylating agent, after a bone marrow tranplanation. Accordingly, the combination of the Sykes and Peach references does not render obvious the claimed methods.

The present invention provides unexpected advantages

Applicants respectfully contend that the cited references do not render the claimed invention *prima facie* obvious. Furthermore, the alleged obviousness is rebutted by evidence of key advantages of the claimed invention (*In re Davies and Hopkins*, 177 U.S.P.Q. 381), namely, that administration of T cell depleted bone marrow, subsequent administration of an alkylating agent that induces mixed hematopoietic chimerism and administration of immunosuppressive composition, corrects hemoglobinopathies and promotes 100% skin graft survival.

The claimed invention teaches a method for inhibiting rejection of solid organ or tissue transplant comprising administering T cell depleted bone marrow; subsequently administering an alkylating agent (for example, busulfan); and an immunosuppressive composition before, during or after transplant.

As discussed in Example 2 and shown in Figures 3A and 3B of the subject application, administration of T cell depleted bone marrow, costimulation blockade and busulfan to β -thalassemic heterozygous mice, corrects hemoglobinopathies in the recipient mice.

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As discussed in Example 3 and shown in Figures 4A and 4B, administration of busulfan five days after the skin-graft resulted in 100% survival of the for at least up to 250 days. Further, at about 100 days post first graft, when recipient mice were regrafted from the same donor mice, 100% of the mice survived for more than 250 days.

The data shown in Examples 2 and 3 of the subject application show unexpected advantages of the claimed invention.

In view of the aforementioned discussion, Applicants respectfully request that the Patent Office reconsider and withdraw the rejection of claims 2-3 under 35 U.S.C. §103.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, Applicants undersigned attorney invites the Office to telephone her at the number provided below.

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No fee, other than the two-month extension fee, is deemed necessary in connection with the filing of this Amendment. If any fee is necessary, the Patent Office is authorized to charge any additional fee to Deposit Account No. 50-0306.

Respectfully submitted,

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EXHIBIT A

U.S. Serial No. 10/057,288
Copy of Receipt Form
issued by the American
Type Culture Collection
confirming deposit of
PTA-2104

ATCC

10801 University Blvd • Manassas, VA 20110-2209 • Telephone: 703-365-2700 • FAX: 703-365-2745

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

Bristol-Myers Squibb Co.
Attn: Robert J. Peach
P.O. Box 4000
Princeton, NJ 08543-4000

Deposited on Behalf of: Bristol-Myers Squibb Company

Identification Reference by Depositor:

Patent Deposit Designation

Plasmid L104EA29Ylg

PTA-2104

The deposit was accompanied by: a scientific description a proposed taxonomic description indicated above.

The deposit was received June 20, 2000 by this International Depository Authority and has been accepted.

AT YOUR REQUEST: We will inform you of requests for the strain for 30 years.

The strain will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strain, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strain.

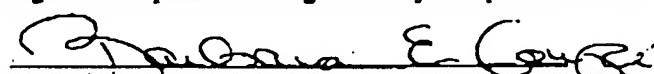
If the culture should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace it with living culture of the same.

The strain will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the culture cited above was tested June 28, 2000. On that date, the culture was viable.

International Depository Authority: American Type Culture Collection, Manassas, VA 20110-2209 USA.

Signature of person having authority to represent ATCC:


Barbara E. Coupé, Administrator, Patent Depository

Date: June 30, 2000

cc: Audrey F. Sher (Ref. Docket D0028)